UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE GENERAL CAUSATION OPINION OF PLAINTIFFS' EXPERT MAHYAR ETMINAN, PHARMD, MSC

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PRELIMINARY STATEMENT

This shotgun *Daubert* motion is set against the backdrop of a well-established scientific and regulatory consensus that NDMA and NDEA are probable human carcinogens. Dr. Etminan's opinions fall directly in line with the weight of authority, grounded upon classic epidemiologic study designs such as case-control, cohort studies, or pooled analysis of the two (meta-analysis) that clearly defined and quantified NDMA or NDEA exposure levels. Dr. Etminan considered and commented on animal studies, mechanistic studies, human dietary studies, occupational exposure studies, human epidemiology studies evaluating health claims data of users of valsartan, and even a study regarding ranitidine. Dr. Etminan reviewed every category of evidence, and the most prominent studies were all considered. Failing to contend with the fact that Dr. Etminan took all of this into account and that his opinions are directly in line with the peer reviewed scientific literature, the Defendants instead resort to mischaracterizations, partial citations, and hyper-technical, but inconsequential attacks on the application of Dr. Etminan's methodology.

In essence, the defense previews a cross-examination that would go to the weight of the conclusions reached, at most, but in no way would establish that Dr. Etminan lacked the necessary qualifications, or that he failed to apply an acceptable scientific methodology. In fact, Dr. Etminan conducted a thorough Bradford Hill analysis.

Defendants did not attack Dr. Etminan's qualifications, as they are more than sufficient. However, Defendants spent 34 pages trying to poke any hole imaginable into Dr. Etminan's methodology. Dr. Etminan is a highly qualified and experienced epidemiologist, his methodology is sound, and thus the motion should be denied.

STATEMENT OF FACTS

NDMA and NDEA have been classified as probable human carcinogens by numerous scientific bodies and regulatory agencies. (Ex. A, Etminan Report at 7). The World Health Organization's 2002 peer-reviewed publication addressing the carcinogenicity of NDMA considered the existing animal studies, mechanistic studies, and human dietary studies, and concluded:

> Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, **NDMA is highly likely to be carcinogenic to humans**.

(Liteplo & Meek, *Concise International Chemical Assessment Document 38 – N-Nitrosodimethylamine*, at 23 (2002), Ex. B, emphasis added (cited in Etminan Report at 7, 35)).[1]

The mechanistic evidence in the peer-reviewed scientific literature is quite strong, for example, a study in monkeys concluded, "primate tissues, especially those of the gastrointestinal and urogenital organs, are sensitive targets for DNA adduct damage due to NDMA, and ethanol co-exposure leads to striking increases in adducts. **Our data support epidemiology implicating nitrosamines in causation of cancers of stomach and other organs, and alcohol as enhancing internal exposure to nitrosamines.**" (Anderson *et al*., *N-nitrosodimethylamine-derived O(6)-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol,* Int. J. Cancer 66, 130-4 (Mar. 1996) Ex. C, emphasis added (cited in Etminan Report at 27, 39).

[1] The occupational literature, valsartan specific epidemiology, and numerous other studies considered by Dr. Etminan did not yet exist in 2002.

A. Dr. Etminan's Background and Qualifications

Dr. Etminan is an Associate Professor of Ophthalmology and Visual Sciences, and an Associate Member at the Departments of Medicine and Pharmacology at the University of British Columbia. Dr. Etminan received a bachelor's degree (BSc) in Pharmacy from the University of British Columbia in 1995, worked as a pharmacist for seven years, and then received his Doctor of Pharmacy degree from Idaho State University. After obtaining a master's degree (MSC) in Clinical Epidemiology at the University of Toronto in 2003, Dr. Etminan held a Post-Doctoral Fellowship and continued his training in Pharmacoepidemiology and Drug Safety at McGill University in Montreal. In 2019, The University of British Columbia Faculty of Medicine awarded Dr. Etminan the distinguished achievement award in clinical research. (Etminan Report at 4).

Dr. Etminan's area of expertise and research is focused on epidemiology, pharmacoepidemiology and causal inference (causation in epidemiology). For the last 20 years, Dr. Etminan has been involved in conducting and publishing pharmacoepidemiologic studies. Dr. Etminan has published over 180 peer-reviewed articles related to drug safety and is a reviewer and consultant on drug safety manuscripts submitted for publication to the Journal of the American Medical Association (JAMA), The British Medical Journal (BMJ), the Canadian Medical Association Journal (CMAJ), British Journal of Clinical Pharmacology, Movement Disorders, and the Journal of the National Cancer Institute. Regarding cancer research, Dr. Etminan published a landmark study on breast cancer and use of nonsteroidal anti-inflammatory drugs in the Journal of the National Cancer Institute, as well as a landmark review on the risk of hair dyes and cancer in JAMA. In the last five years, Dr. Etminan has published multiple landmark studies applying the principles of causation in epidemiology (also known as causal inference) to drug safety studies. (Etminan Report at 5).

Furthermore, Dr. Etminan has acted as a drug safety consultant to numerous drug

regulatory agencies, such as the Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency. Dr. Etminan's work with drug regulatory agencies has led to the publication of warning letters intended to notify physicians of risks associated with certain drugs. (Etminan Report at 5).

B. Dr. Etminan's Study Inclusion and Exclusion Criteria were Proper

Defendants' main attacks on Dr. Etminan are premised on mischaracterizing Dr. Etminan's study inclusion and exclusion criteria as improper and crafted to reach a predetermined conclusion. (Def. Br. at 7). The study inclusion and exclusion criteria that Defendants criticize were designed to produce the most reliable epidemiological data, focused on the exposure levels (dose) that can be quantified or estimated to a reasonable degree of accuracy. Below are Dr. Etminan's study inclusion and exclusion criteria that Defendants have mischaracterized to the Court as "outcome-based and inherently biased":

Study Inclusion Criteria:

- ***Clearly*** defined and ***quantified*** nitrosamine compounds…
- … These studies also had to be able to ***differentiate*** NDMA or NDEA specific valsartan batches (***from valsartan batches that did not contain excessive amounts of NDMA or NDEA***).

Study Exclusion Criteria:

- Dietary or occupational studies that ***did not specifically quantify the amount*** of nitrosamines or NDMA concentrations.

(Etminan Report at 13 (emphasis added)). Indeed, Dr. Etminan's logical requirement to ensure that exposure levels are adequately quantified resulted in the desired result. Unsurprisingly, some of those excluded studies that did not quantify exposure were not able to demonstrate a statistically

significant increased risk of cancer. As a result, Defendants complain that Dr. Etminan must have purposefully crafted his exclusion criteria to exclude literature "that show no statistically significant association", and what the Defendants erroneously believe are the "most relevant epidemiologic literature". (Def. Br. at 6-7, 18).

Contrary to Defendants' misleading arguments, Dr. Etminan applied his well-reasoned inclusion and exclusion criteria equally to all studies, be they dietary, occupation, or valsartan specific studies, and without consideration of the study results, and did include negative studies as well. (Etminan Report at 13). In deposition, Dr. Etminan clearly testified, "First of all, I – I included three negative studies because they included my – they met my search criteria in my report. And so I had to talk about them, and I – they were negative, and I had to talk about the limitations." (Etminan Dep. Tr. Vol. I, 211:8-13, Ex. D).

After a thorough review of the extensive amount of literature remaining after applying Dr. Etminan's exposure quantification requirements, the scientific literature is clear and enabled Dr. Etminan to confidently opine:

> The preponderance of basic scientific evidence, as well as evidence from well-designed occupational and dietary epidemiologic studies with long-follow ups and dose-response analysis, are **strongly suggestive** of a causal link between NDMA intake and the following cancers: esophageal, stomach, colon, liver, pancreas, lung, bladder, prostate, and blood (leukemia, lymphoma multiple myeloma). It is my opinion expressed with a reasonable degree of scientific certainty that NDMA in valsartan can cause the preceding 9 cancers.

(Etminan Report at 32 (emphasis added)).

Dr. Etminan explains in his expert report how studies with a "lack of quantifying or categorizing (low vs high) NDMA/NDEA amounts in these studies will make it difficult to necessarily draw a causal link between NDMA/NDEA and cancer," as part of his epidemiology methodology (Etminan Report at 13). Throughout his report Dr. Etminan also explains how well-

designed studies that quantify and stratify exposure and follow a large number of patients for decades will increase the power of the study, so that the study can detect statistically significant increases in rarer types of cancer and produce more reliable results. (Etminan Report at 11-12, 20-23; Etminan Dep. Tr. Vol. I, 211:24-212:1). As a result, Dr. Etminan included a 2019 occupational study by *Hidajat*, the strongest and most comprehensive evidence of NDMA carcinogenicity in humans to date. *Hidajat* found NDMA exposure resulted in "a statistically significant **increase in the risk of the following cancer deaths: stomach, esophageal, pancreatic, bladder, liver, lung, prostate, and blood cancers (lymphoma, leukemia, multiple myeloma)**." (Etminan Report at 14).

Predictably, Defendants resorted to attacking Dr. Etminan's inclusion and exclusion criteria. In a brazen double down, Defendants contend that Dr. Etminan's opinions regarding NDMA or NDEA causing cancer "do not fit this case" because Dr. Etminan did not exclude human NDMA or NDEA studies where the exposure was longer, or the dose was higher than what Plaintiffs were exposed to from contaminated valsartan. (Def. Br. at 6). However, a foundational issue in this case is if NDMA is even carcinogenic to humans, and if so, what organs are susceptible.[2] Therefore, *Hidajat* is absolutely on point, and Dr. Etminan's opinions undoubtedly "fit this case." Furthermore, Plaintiffs' experts Dr. Panigrahy and Dr. Madigan confirm that the lifetime cumulative exposure levels of NDMA in *Hidajat* and the dietary studies are reached by Plaintiffs ingesting NDMA contaminated valsartan.

Tellingly, Defendants don't critique Dr. Etminan for excluding any studies that quantified

[2] It is Plaintiffs position that the workers lifetime cumulative exposure to NDMA in *Hidajat* is comparable to Plaintiffs' lifetime cumulative exposure to NDMA due to contaminated valsartan. Regardless, the cumulative exposure levels are issues of fact, and should go to the weight of the evidence.

NDMA or NDEA exposure to a reasonable degree of accuracy.

LEGAL ARGUMENT

I. DR. ETMINAN IS WELL QUALIFIED

The Third Circuit, "made clear in *Paoli II,* an expert's level of expertise may affect the reliability of the expert's opinion." *Elcock v. Kmart Corp*., 233 F.3d 734, 746 (quoting *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 741 (3d Cir. 1994) ("*Paoli II*")). Defendants do not attack Dr. Etminan's extensive qualifications, which are set forth in detail above and strongly support a finding of reliability.

II. DR. ETMINAN'S METHODOLOGY IS RELIABLE

The admissibility of expert testimony is determined pursuant to Rule 702, which incorporates the *Daubert* standard.

> In determining reliability, a court may look to several non-exhaustive factors, including:
>
> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Geiss v. Target Corp., 2013 WL 4675377 at *4 (D.N.J. 2013) (quoting *Elcock v. Kmart Corp.*, 233 F.3d 734, 745-47 (3d Cir. 2000) (Ex. E). In applying the Daubert standards, Courts are cognizant that, "Rule 702 has a liberal policy of admissibility." *Geiss*, 2013 WL 4675377 at *4 (citing *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008), other citations omitted. Dr. Etminan took into account the full spectrum of scientific evidence on the issue, including animal studies, mechanistic studies, human dietary studies, as well as the recent occupational literature addressing NDMA carcinogenicity, and recently published epidemiological literature addressing people who

used valsartan.[3] Dr. Etminan applied the Bradford-Hill viewpoints/criteria in evaluating the carcinogenicity of NDMA and NDEA. (*See* Etminan Report at 3, 9, 13, 26-29; Etminan Dep. Tr. Vol. I, 15:10-21, 17:12-15, 133:21-134:4, 160:10-23, 165:23-166:3, 169:14-25; 171:11-172:9, 177:7-20, 181:24-182:14, 185:3-15, 187:6-17, 188:1-16, 188:25-189:7, 189:13-21, 221:5-212:15). Dr. Etminan's opinions are based squarely upon and within a large body of peer-reviewed literature and he is well-qualified, thus the opinions easily satisfy these criteria.

Daubert requires that an expert, whether basing his opinions upon studies or personal experience, "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Elcock*, 233 F.3d at 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)). Dr. Etminan applied the methods and knowledge he uses in his clinical and academic work to offer an opinion that has also been expressed in peer reviewed medical literature describing real world experiments and studies, clearly satisfying these standards. When asked if a Bradford Hill analysis is something that he does in his professional capacity outside of litigation, Dr. Etminan testified,

> I mean, I use the criteria set by Bradford Hill to when I'm look for – or asking questions as part of my research on whether Drug A cause, you know, outcome Y, because I feel like it is relatively complete, and it has a lot of the sort of variables that one needs to consider when deciding on the [causal question].

(Etminan Dep. Tr. Vol. I, 160:10-161:1). Furthermore, when asked how he determines what variables need to be adjusted for in a study, Dr. Etminan replied,

> Well, that's an area that actually I have been working on for the past few years, and I have been advocating. So what one of the – sort of up-and-coming methods is the use of what we call "causal diagrams" where we draw – draw out all the common causes of whatever the question is, whether it – exposure on health that you're look at. We draw all the common causes for that questions, and then we find which –

[3] This stands in stark contrast to the defense experts, who uniformly failed to appropriately consider the cross-section of significant categories of scientific evidence directly relevant to the question of general causation.

> which are the paths – what we call "biasing paths" that need to be adjusted for or blocked.

(Etminan Dep. Tr. Vol. I, 31:15-32:2).

Instead of acknowledging that Dr. Etminan applied the same well-reasoned methodology in this litigation as he does in his clinical and academic work, Defendants baselessly claim that Dr. Etminan imposed "arbitrary requirements" with "no scientific reason" to "exclude relevant studies demonstrating no statistically significant increased risk of cancer from NDMA in valsartan in favor of less relevant diet and occupational studies". (Def. Br. at 14-15). Interestingly, in Defendants' motion to exclude Dr. Lagana, Defendants falsely suggested that Dr. Etminan rejected the dietary literature as unreliable. (Def. Lanaga Br. at 16).

A. <u>Dr. Etminan Applied Well-Accepted Methodologies in Forming His Opinions</u>

Dr. Etminan applied the Bradford Hill viewpoints/criteria, which is a well-accepted methodology in the Third Circuit: "we accept that the Bradford-Hill and weight of evidence analyses are generally reliable." *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 796-797 (3rd Cir. 2017). Dr. Etminan's analysis was more than sufficient from a methodological standpoint, and the Defendants cannot come close to meeting the standard for exclusion: "A court should not, however, usurp the role of the fact-finder; instead, an expert should only be excluded if the flaw is large enough that the expert lacks the 'good grounds' for his or her conclusions." *Zoloft*, 858 F.3d at 792-793.

In conducting his Bradford Hill analysis, Dr. Etminan factored in every category of relevant scientific data presented in the peer-reviewed literature, including the animal studies, human dietary studies, mechanistic studies, occupational exposure literature, and human epidemiology studies involving users of valsartan (and even ranitidine). (Etminan Report). In *Zoloft,* regarding the materials considered by the expert in that litigation, the Court observed that, "the particular

combination of evidence considered and weighed here has not been subjected to peer review," (*Zoloft*, 858 F.3d at 797). That contrasts with this case, where this has been done, including by the WHO, and across peer-reviewed literature – every study relied on by Dr. Etminan is peer-reviewed. Dr. Etminan's application of this methodology is fully in line with the peer-reviewed literature, as he clearly considered each category of evidence, including countervailing studies, and explained how each fit into his overall analysis. Dr. Etminan explained his methodology to identify epidemiologic studies of NDMA and cancer:

> I understood a search of the medical literature using standard and accepted methodology, which includes a systemic search of the literature and accepted Medical Subject Headings (**MeSH**) using specific inclusion and exclusion criteria. Published epidemiologic studies that met the inclusion criteria were identified. Studies were reviewed focusing on both strengths and limitations of each study.

(Etminan Report at 12).

Of import, Dr. Etminan not only analyzed studies that supported his opinion, but he also addressed and factored in arguably negative or equivocal studies. Contrary to Defendants' allegation that Dr. Etminan "simply cherry-picks certain studies that support his ultimate conclusions that NDMA and NDEA cause all nine types of cancer" (Def. Br. at 23), Dr. Etminan clearly explained in his deposition after the Defendants attempted to misrepresent his methodology and the totality of evidence that:

> So totality doesn't mean just looking at what – how many positive studies you have and how many negative studies you have. First of all I – **I included three negative studies** because they included my – they met my search criteria in my report. And so I had to talk about them, and I – **they were negative, and I had to talk about the limitations**.
>
> And one of those three studies is Straif that – that you mentioned, could not – with 15 cases, could not really study the questions. So it wasn't really a negative study. It wasn't a well-designed study that led to a negative results. It was a very small study that could not answer the question.

> Fritschi also combined different exposures. I talked about the limitations of that study. And the – when I say totality, yes, I believe that the study by Hidajat carries more of the weight because it was very long follow-up, good sample size.

(Etminan Dep. Tr. Vol. I, 211:5-212:1(emphasis added)). For example, when discussing the occupational studies addressing NDMA and pancreatic cancer, Dr. Etminan provided the following analysis:

> The study by *Straif* was underpowered to appropriately examine pancreatic cancer deaths, as the study only identified 15 pancreatic cancer deaths. The risk of death due to pancreatic cancer after NDMA exposure in *Hidajat* was shown to increase by approximately 2.5 times among those exposed to high intake of NDMA (HR=2.6%, 95% CI: 1.94-3.49). *Hidajat's* study was a significantly more powered study compared to *Straif*, as Hidajat had a much larger pool of subjects and subsequently a much higher number of pancreatic cancer death cases (328 v 15). Additionally, Hidajat had an increased follow-up time compared to *Straif*. For these reasons, *Hidajat* was able to detect the increased risk of death due to pancreatic cancer when exposed to high dose of NDMA.

(Etminan Report at 19-20). This approach more than suffices to establish, "a scientific method of weighting that is used and explained." *Zoloft*, 858 F.3d at 796.

B. Dr. Etminan's Methodology is Consistent With Widely Accepted Standards for Statistical Significance

Consistent with all their attacks on Dr. Etminan, Defendants also misconstrue Dr. Etminan's report and testimony related to statistical significance, claiming that "rather than recognize a statistical threshold that must be met to establish causation, Dr. Etminan hypothesizes that causation *may* exist where it cannot be disproven under his contrived standard." (Def. Br. at 21). In reality, Dr. Etminan opined:

> Almost all the studies identified in this review have shown an increase in the risk of NDMA with different types of cancer[4] (with one positive study with NDEA and pancreatic cancer). ***Some* of these studies did show an increase in risk that did not reach statistical significance**. The main reason for the non statistically significant results might have been due to a relatively short follow up, differences

[4] Every dietary study identified by Dr. Fryzek (Defendants' epidemiologist) demonstrated an increased risk of different types of cancer with exposure to NDMA. (Fryzek Report at 21-31, Ex. F; Pl. Fryzek Br. at 12-17).

> in the types of questionnaires used, and a small number of total events (sample size) compared to the number of potential confounders adjusted for in the studies which can lead to model overfitting resulting in imprecise results. Another potential reason might be due to inadequate cancer latency or the time required for the cancer process to complete and lead to symptomatic disease. Although latency has an important role in the cancer process, it must be noted that cancer latency can have a wide range. In animals, NDMA has shown to cause cancer in as little as 36 weeks. In humans, the antidiabetic drug pioglitazone, a potential carcinogen that acts as a promoter similar to NDMA has shown in well designed epidemiologic studies to increase the risk of cancer even after one year of use

(Etminan Report at 31(emphasis added)). Dr. Etminan repeatedly goes into detail throughout his report explaining how the non-statistically significant results from underpowered studies supplement the well-powered studies that elucidate statistically significant increases in the risk of cancer due to NDMA:

> As with most findings in Straif, the data on bladder cancer was also inconclusive (RR=1.3, 95% CI: 0.4-5.0) and could not exclude an elevated risk. And yet again, as a result of *Hidajat* being more well-powered and designed study which included better ascertainment of competing events and the longest follow up of all epidemiologic studies (that have examined the risk of cancer with NDMA), it was able to detect a statistically significant increase in the risk of bladder cancer deaths of approximately three-folds or 182% increase due to NDMA exposure (RR=2.82, 95% CI: 2.16-3.67), which *Straif* was unable to produce statistically significant results.
>
> **The increased risk (which is not statistically significant) in the dietary studies is consistent with the statistically significant increased risk demonstrated in Hidajat**.

(Etminan Report at 22). Dr. Etminan provided a similar logical analysis regarding the statistical significance of the studies that investigated the risk of NDMA and prostate cancer:

> The study by *Straif* showed a doubling of the risk of prostate cancer, but the result was not statistically significant (RR=2.1, 95% CI: 0.7-6.2). Finally, due to the superiority of *Hidajat* as stated above, a statistically significant increased risk of death due to prostate cancer was apparent (HR=5.36, 95% CI: 4.27-6.73) by a factor of 5 or 436% among those exposed to the highest NDMA levels compared to the lowest NDMA exposure group.
>
> **The increased risk of prostate cancer (which not statistically significant) in the dietary studies is consistent with the increased risk demonstrated in Hidajat.**

(Etminan Report at 23).

A study does not need to reach statistical significance for an expert to rely in part on the study in providing an opinion. "A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power… A standard based on replication of statistically significant findings obscures the essential issue: a causal connection. Given this, the requisite proof necessary to establish causation will vary greatly case by case." *In re Zoloft*, 858 F.3d at 794. As demonstrated above, the non-statistically significant studies further support and complement the statistically significant studies. Thus, Defendants have requested the Court preclude Dr. Etminan from offering "any opinions concerning statistical significance or the statistical significance of any particular study finding (*see* Report at 12) (disregarding accepted standards on statistical significance and asserting that a study's results are not 'necessarily negative' where its confidence interval is inclusive of 1.0)." (Def. Br. at 3-4). Defendants go on to falsely claim Dr. Etminan "creates his own statistical standard that a confidence interval inclusive of 1.5 or greater denotes *possible* causation." (Def. Br. at 20). Defendants cite to page 12 of Dr. Etminan's expert report, where he devoted an entire section to explain how to properly interpret statistical significance, with supporting citations:

> However, in a situation where the RR is 2.0 but the confidence interval included a value that was less than 1.0 (e.g. 0.5-4.0), then it could be inferred that the carcinogen increases the risk by a value of 2.0, but the results are not statistically significant, as the lower bound of the confidence interval also includes 1.00 (no effect). This happens, for the most part, due to a small number of events which is a function of an inadequately small sample size. These results can be interpreted as inconclusive or imprecise, as the RR can be as low as 0.5 (protective) or as high as 4.0 and more likely than not (based on a confidence interval of 0.5-4.0) if the study was repeated that the RR will be greater than 1.0.
>
> Thus, in studies where the magnitude of the measure or effect (OR, RR, HR) has a wide confidence interval, where this range can fall partly within the range of no effect (lower end) but at the same time the upper end of this value can fall in the clinically meaningful effect (e.g., RR>1.0), then one can not conclude that the

> results of the study are necessarily negative (i.e., a specific carcinogen does not increase the risk of cancer). **While one could interpret the results as inconclusive, it would be *improper* to conclude that the carcinogen was not harmful**.

(Etminan Report at 11-12 (emphasis added)).

As an aside, Defendants partially quoted Dr. Etminan to create the false impression that Dr. Etminan doesn't understand "well-established statistical standards to evaluate general causation." (Def. Br. at 20). A quick review of the deposition transcript reveals that Dr. Etminan has a deep understanding of statistical significance and its relation to epidemiology (Defendants extremely misleading partial quote is bolded):

> Q: What does the term "statistically significant" mean from an epidemiological standpoint?
>
> A: Actually, it's – that's a great question. So for many, believe that the statistically significant means the results of a study are – for example, if the P value is large and the results are not statistically significant, that means that the – there is really no effect associated with that – that exposure, carcinogen.
>
> But in reality, this is really not the case. And the American Statistical Association, in 2016, published commentary to sort of clear the water on the issue.
>
> So the correct interpretation of your question on statistical significance means that if some – if an effect size of a – from a study is not statistically significant, that means that it does not deviate from the statistical model and assumptions that it – that it carries with it.
>
> It does not have anything – it does not say anything at all about whether, you know that particular exposure of a study and the outcome are related or associated. That's – that's all it means, that the – the data and the assumptions around that data for that analysis do not deviate.
>
> Q: So what does that mean, to say that "the data and the assumptions do not deviate"?
>
> A: Again, in more simple terms, when we do a study, there are – the data that we use. The type of a statistical model that we use carries with it a number of assumptions.
>
> And if – if the results are statistically significant, all it means is that your data, the data that you have from that study, are, if you will, different than – than – than the model that you're using, provided that all other assumptions are met.
>
> So it's more about whether the data fits in the assumptions or not. It's not about – statistically significant means that, yes, this exposure causes this outcome,

> or if it's not significant, it means it doesn't. That's not what a statistical significant means at all.
> **Q: So statistical significance – are you saying – what I understand you to be saying is that statistical significance is not evidence of causation?**
>
> **A: Yeah, it's – statistical significance doesn't have anything to do with causation.** Statistical significance, again, means how similar is my data to the statistical model that I'm using provided all other – all the assumptions that need to be met are met. Sometimes they are not. But do the assumptions have to – to be met, so again, there are caveats.
>
> It also – statistical significance also is a reflection of precision as well. Studies with a large sample size are – are more precise in terms of the – let's say, the confidence interval around the effect size because there are very large sample sizes. Usually, they have higher events.
>
> Smaller studies with lower sample size and lower events usually have a wider confidence interval or a larger P value because of – they're – they're more imprecise. So, again, statistical significance and whether an exposure is causing an outcome are different – are two different entities.

(Etminan Dep. Tr. Vol. I, 27:14-30:15).

Furthermore, in the Third Circuit, an expert's opinion is admissible, if the process or technique used is reliable, and the methods and procedures are based on science "rather than on the subjective belief or unsupported speculation". *In re Paoli*, 35 F.3d at 742; *In re Johnson & Johnson Talc Powder Prods. Mktg., Sales Practices & Prods. Litig.* 509 F. Supp. 3d at 131. In the case of *In re Johnson & Johnson Talcum Powder,* 509 F. Supp. 3d 116 (2020), the District of New Jersey was faced with admissibility of expert testimony for general causation. Opining that the use of talc can cause ovarian cancer, Plaintiffs' expert considered a wide body of relevant epidemiological evidence, including "statistical data, strengths and weaknesses of study type, effect of bias, chance, confounding and differences in exposure measures. She considered dose response, data from non-epidemiologic lines of evidence such as animal, cell, clinical and pathological studies." *Id* at 525. Ultimately, Plaintiffs' expert found a relative risk factor of 1.2 to 1.6, which the Court held was sufficient for purposes of general causation. *Id* at 575. The Court opined that "[i]n epidemiology, **there is, however, no threshold, or a magical number, of a**

relative risk that must be found in order to place significant weight on the strength of association factor." Indeed, "[a] relative risk of 2.0 is not so much a password to a finding of causation as one piece of the evidence, among others for the court to consider in determining whether an expert has employed a sound methodology in reaching his or her conclusion." *Id* at 538 (Citing *Magistrini*, 180 F. Supp. 2d at 606 (quoting *Landrigan v. Celotex Corp.*, 127 N.J. 404, 419, 605 A.2d 1079 (1992) (emphasis added)).

Dr. Etminan has a deep understanding of statistical significance, what can impact statistical significance, and what weight to give studies with varying degrees of statistical significance, and applied that knowledge in a scientifically reasoned manner. It would be improper for the Court to preclude Dr. Etminan from offering opinions related to statistical significance.

C. <u>Dr. Etminan Reliably Applied Bradford Hill</u>

Dr. Etminan's application of Bradford Hill was clearly reliable. Defendants attempt to criticize Dr. Etminan's application of Bradford Hill by correctly noting that "In analyzing the 'analogy,' criterion – whether similar compounds also cause the same outcome, Dr. Etminan cites only a single study finding an association between nitrites (a potential dietary precursor of NDMA) and cancer". (Def. Br. at 24). Even though this argument would clearly go to the weight and not the admissibility of Dr. Etminan's opinion, it is being addressed because it is yet again misleading. While it is correct that Dr. Etminan provided a single citation within the "analogy" paragraph to nitrites increasing the risk of cancer, a simple search for the word "nitrite" within Dr. Etminan's expert report reveals five citations to studies demonstrating an increased risk of cancer due to nitrites. (Etminan Report at 27, 36-39). Instead of exploring this issue at deposition before making misleading statements in their motion, Defendants merely asked Dr. Etminan for his understanding of how the analogy factor is applied, to which he replied:

> Right. So analogy means that is there any evidence that carcinogens that are similar chemically, you know, similar in the chemical structure of the carcinogen in question also cause cancer. So sometimes people refer to it as a class effect, for example. So if one drug can cause an adverse event, then that – sometimes, it's a class effect so that group of drugs in that class of drugs can also cause that adverse event, which strengthens the analogy – analogy argument. But it generally means whether – if we talk about the carcinogen, whether other carcinogens that are similar in structure also – have also shown to cause cancer.

(Etminan Dep. Tr. Vol. I, 176:23-177:20). Assuming Defendants somehow were not aware of the plethora of studies demonstrating nitrites increase the risk of cancer, the proper place for Defendants to have explored this issue, that would merely go to the weight of Dr. Etminan's opinions, would have been during his deposition.

Defendants then identify their main argument as to why they believe Dr. Etminan's application of Bradford Hill is unreliable, "*Most tellingly*, Table 2 of Dr. Etminan's report, which he uses to demonstrate that **seven of the nine** Bradford Hill Criteria weigh in favor of causation for all nine cancers, **is based on just one study** – Hidajat." (Def. Br. at 24 (emphasis added)). What is actually most telling, is that Defendants again make an extreme misrepresentation, that even if true, would only go to the weight of Dr. Etminan's opinions. First, Dr. Etminan included numbers from *Hidajat* on **two of the nine** Bradford Hill Criteria (Dose Response and Strength of Evidence), because *Hidajat* provided a longer follow up time and demonstrated a dose response relationship for all nine cancers, which made *Hidajat* the easiest to use in his graph that summarizes his extensive analysis immediately preceding in his expert report. Even assuming Defendants never read the preceding pages of Dr. Etminan's export report and instead went straight to the chart, directly below the chart is states "**Dose response data for dietary studies are *provided in section 9.0* and demonstrate a similar trend**." (Etminan Report at 29 (emphasis added)). Making Defendants' misrepresentation even more striking is that Defendants actually explored this issue at deposition and Dr. Etminan answered, "I have included the Hidajat [study]

because I felt that it satisfies this criteria more than the – in this table. **But I have included the – *the data from the dietary studies* in my assessment from all the variables as well**." (Etminan Dep. Tr. Vol. I, 179:10-14 (emphasis added)). Furthermore, Dr. Etminan provides 12 citations within the section of his report on the presence of a dose response relation, opining in part:

> **Moreover, *dietary epidemiologic studies* on stomach cancer, pancreatic cancer, head and neck cancers, colon cancer, lung cancer, and blood cancers *have also shown a positive dose response relation***. The dietary study by *Jakszyn* for prostate cancer and bladder cancer found an increase in the risk of both cancers with higher doses of NDMA, but the results did not reach statistical significance potentially due to small number of events. Data from large epidemiologic studies that specifically examined the effect of prolonged NDMA exposure through diet are not available for liver cancer. **Overall, presence of a dose response mainly driven by *Hidajat* but *also present in dietary epidemiologic studies* play a significant role in demonstrating a causal link between NDMA/NDEA in valsartan and cancer**.

(Etminan Report at 27-28).

Even Dr. Fryzek, Defendants' epidemiologist, quoted five dietary studies within the report he submitted which specifically note detecting a dose-response relationship between NDMA exposure and the risk of numerous types of cancer. (Fryzek Report at 22, 24, 26, 27, 30).

Defendants' attacks on the reliability of Dr. Etminan's application of Bradford Hill are gross misrepresentations, that even if accurate would only go to the weight of Dr. Etminan's opinions. In *Glynn*, the Daubert motion to preclude plaintiffs' expert on general causation was denied because, as here, the expert considered the Bradford Hill factors, and the criticisms went to the weight, not admissibility of the testimony, the Court concluded, "Defendant is free to address these issues on cross-examination…" *Glynn v. Merck Sharp & Dohme Corp*., 2013 WL 1558690, at *4 (D.N.J. April 10, 2013). The same applies here.

D. Valsartan Human Epidemiology Studies

Defendants again attempt to deceive this Court, this time into believing that Dr. Etminan **did not consider** *Pottegard* and *Gomm*, two poorly designed studies which attempted to

investigate valsartan's impact on the risk of cancer. (Def. Br. at 14). Defendants cite to page 13 of Dr. Etminan's expert report for support that he did not consider *Pottegard* or *Gomm*. However, page 13 of Dr. Etminan's expert report reveals that *Pottegard* and *Gomm* "***were reviewed but were not weighted strongly*** when assessing the risk of cancer with NDMA exposure." (Etminan Report at 13).

1. Pottegard

Contrary to what Defendants have led this Court to believe, Dr. Etminan actually provided a detailed critique of *Pottegard* and why he gave the study little weight. (Etminan Report at 24-25). Dr. Etminan's main critique of *Pottegard* is that the study compared "subjects of *possibly* took valsartan containing NDMA" and "compared their risk of cancer to subjects that the investigators *believed* were unlikely to have ingested valsartan containing NDMA (at the time of the study by Pottegard, the understanding as to the extent and degree of valsartan contamination was still in its infancy). (Etminan Report at 24-25). Defendants do not dispute in their brief that Pottegard examined patients "who had consumed prescribed valsartan that ***potentially*** contained NDMA." (Def. Br. at 14 (emphasis added)). Dr. Etminan continues, elaborating on why *Pottegard* was unable to estimate or quantify NDMA exposure to a reasonable degree of accuracy, and the resulting impacts:

> All subjects who possibly ingested NDMA contaminated valsartan were grouped together as ***the authors looked at the cumulative dose of valsartan (mg of the pill) as the unit of analysis and not the cumulative amount of NDMA (which is the actual exposure of interest)***. This limitation will undoubtably lead to misclassification of exposure as the varying amounts of NDMA from different batches and manufacturers is not accounted for using this approach since the study's hypothesis was that higher doses of NDMA will cause cancer and not higher doses of valsartan per se. Due to this limitation, one could reasonably anticipate that the study would not produce statistically significant harmful effect of NDMA with cancer and would have missed a possible risk of cancer with valsartan contaminated NDMA.

(Etminan Report at 25 (emphasis added)). Again, Defendants concede in their brief that *Pottegard* looked at "cumulative dose of valsartan", and not cumulative amount of NDMA exposure. (Def. Br. at 14). Dr. Etminan goes on to explain why grouping based on cumulative dose of valsartan instead of cumulative dose of NDMA will result in exposure misclassification and false negatives:

> Daily doses of valsartan (80mg, 160mg, 320mg) were utilized in an attempt to quantify NDMA exposure and stratify the results based on cumulative NDMA exposure. The notion that the level of NDMA contamination will increase as the milligram of the valsartan pill increase, is only true when all pills are made from the same contaminated batch of active pharmaceutical ingredients (API). What has been discovered since the publication of *Pottegard* is that ***batches of API can vary by orders of magnitude on their level of NDMA contamination. As such, an 80mg tablet of valsartan can have substantially higher levels of NDMA in it than a 320mg tablet***. These discrepancies can lead to exposure misclassification, resulting in false negatives.

(Etminan Report at 25 (emphasis added)).

2. <u>Gomm</u>

As with *Pottegard*, Dr. Etminan also provided a detailed critique of *Gomm* and why he gave the study very little weight. (Etminan Report at 26). Of note, Defendants acknowledge that just like *Pottegard*, *Gomm* examined patients "who had consumed prescribed valsartan that *potentially* contained NDMA" and assumed NDMA exposure "based on cumulative dose of valsartan". (Def. Br. at 14 (emphasis added)). Predictably, Dr. Etminan also found *Gomm's* inability to estimate NDMA exposure to a reasonable degree of accuracy a significant weakness:

> Similar to the *Pottegard* study, the study by *Gomm* could not specifically identify the true NDMA levels of the various batches, and **the dose-response analysis only looked at cumulative dose of valsartan *per se* and not the cumulative NDMA content in the valsartan formulations (mg of pill vs. ng of NDMA in pill)**.

(Etminan Report at 26).

Not only do Defendants misrepresent the consideration and thorough analysis Dr. Etminan gave to *Gomm*, but Defendants also misrepresent the results of *Gomm*. Defendants desperately want this Court to believe that *Gomm* "***observed no statistically significant increased risk of***

cancer due to NDMA-containing valsartan." (Def. Br. at 14). However, *Gomm* concluded "a statistically significant association was found, however, between exposure to NDMA-contaminated valsartan and hepatic cancer (adjusted HR 1.16; 95% confidence interval [1.03; 1.31])." (*Gomm*, Ex. G; Etminan Report at 26).

Defendants' representations that Dr. Etminan did not consider *Gomm* or *Pottegard*, and that *Gomm* did not find a statistically significant increased risk of cancer due to NDMA-containing valsartan are patently false. Dr. Etminan not only considered *Gomm* and *Pottegard*, but he also provided a detailed critique of each. Furthermore, *Gomm* explicitly detected a statistically significant association between exposure to NDMA-contaminated valsartan and liver cancer. Dr. Etminan's analysis of *Gomm* and *Pottegard*, and the amount of weight he assigned to each, are issues of fact that go to the weight not the admissibility of Dr. Etminan's opinions.

E. <u>Dr. Etminan's Opinions "Fit" the Case</u>

Defendants cite a case out of the Second Circuit holding, "[I]n a toxic tort case, expert testimony on the issue of general causation meets Rule 702's 'fit' requirement only if the testimony includes an opinion that (1) exposure to the particular substance at issue, (2) in the dose to which the plaintiff was exposed, (3) for the duration in which plaintiff was exposed, (4) can cause the particular condition(s) of which the plaintiff complains." *Amorgianos v. Nat'l R.R. Passenger Corp*., 137 F. Supp. 2d 147, 163 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002). (Def. Br. at 6). Dr. Etminan provided an opinion that does precisely that:

> The dose relation with NDMA and cancer has strong implications to the **NDMA contained in some batches of valsartan**, as some of these batches have been tested to have as high as **288 times higher NDMA content than some of the *highest* NDMA dose category in published dietary epidemiologic studies** of NDMA. Thus, the risk of cancer in subjects exposed to high levels of NDMA in valsartan for potentially long-periods (**used for many months**), has a high likelihood of increasing the risk of the **aforementioned 9 cancers** in these individuals.

(Etminan Report at 28 (emphasis added)).

Regardless of how Defendants construe their argument, Dr. Etminan compared the daily dose of NDMA and NDEA in dietary studies with exposure levels in valsartan over 10 times in his expert report, and typically in bold so that it would stand out. (Etminan Report at 16, 18, 20, 21, 24, 28, 31, 32). For example:

> A case-control study from France by *Pobel* showed an increase in the risk of gastric cancer with higher NDMA exposure (OR=7.00, 95% CI: 1.85-26.46) which was defined as 290ng/day or more **(180 times lower than the 52,500ng found in some of the 320mg tablets of valsartan)**.

(Etminan Report at 18). For the sake of brevity, only one additional example will be given to illustrate the lack of foundation to Defendants' argument:

> A 1995 study *La Vecchia* showed that those who took ≥190 (ng/day) of NDMA had a 37% increased risk of developing stomach cancer (OR=1.37, 95% CI: 1.1-1.70) than those taking ≤130 (ng/day)[5] when controlling for a number of potential confounding variables, including family history of stomach cancer. **Of note, the daily NDMA amount in some of the manufactured batches of valsartan are as high as 52,500 ng in one 320mg tablet of valsartan, which would be 276 times higher than the high dose category defined in the *La Vecchia* study**.

(Etminan Report at 16).

Dr. Etminan also explains that due to individual variability, cancer latency can have a wide range, resulting in some individuals developing cancer in a matter of months after NDMA exposure, while others could take many years to develop cancer. Dr. Etminan notes that individual variability in cancer latency can be impacted by dose (increased dose decreases duration needed),[6] age, genetics, immune system status, and more. (Etminan Report at 31). Dr. Etminan also explained that even though some individuals will quickly develop cancer after NDMA exposure, because some individuals will take many years, it is necessary for studies to have many years of

[5] Interestingly, the FDA considers >96 nanograms of NDMA per day to not be reasonably safe, and *La Vecchia* detected a statistically significant increased risk of cancer at only slightly higher daily doses.

[6] The interplay between NDMA dose and duration is why Dr. Madigan calculated Lifetime Cumulative Exposure to NDMA in the various epidemiological studies.

follow-up in order to fully capture the actual increased risk of cancer due to NDMA exposure. (Etminan Report at 26, 31; Etminan Dep. Tr. Vol. II, 51:23-52:4, 61:7-14, Ex. H). Furthermore, studies such as *Hidajat* had an endpoint of cancer *deaths*, not cancer formation. (Etminan Report at 14; Etminan Dep. Tr. Vol. I, 94:7-11; Etminan Dep. Tr. Vol. II, 99:25-100:17). Obviously, it takes longer for cancer to develop and then ultimately kill a person than it does for cancer to just develop.

Any arguments that Dr. Etminan's opinions do not fit this case or that Dr. Etminan did not consider the substance, dose, and duration of the exposure in relation to the particular conditions at issue are without merit.

F. The Hidajat Occupational Study Most Accurately Quantifies NDMA Exposure

The largest occupational study with the longest follow up that has specifically examined NDMA with respect to different types of cancer deaths was a 2019 study by *Hidajat*.[7] As with all Plaintiffs' experts, Defendants criticize Dr. Etminan for relying on *Hidajat*. Defendants first attack Dr. Etminan's study inclusion and exclusion criteria for capturing *Hidajat*. (Discussed *supra* at 4-6). However, Dr. Etminan's criteria in question was properly crafted to ensure NMDA dose was quantified. (Etminan Report at 13). Importantly, Dr. Etminan notes that compared to all other epidemiologic studies examining "the risk of NDMA and cancer, quantification of NDMA exposure information was significantly more robust in the study by *Hidajat*." (Etminan Report at 14).

[7] Of note, the strongest human epidemiological study on NDMA and cancer, *Hidajat*, was published after the International Agency for Research on Cancer (1978), U.S. EPA (1987), Agency for Toxic Substances and Disease Registry (1989), World Health Organization (2002), and National Toxicology Program (2016), made their determinations as to the level of evidence that NDMA is carcinogenic to humans. (Fryzek Dep. Tr. 424:5-432:5, Ex. I).

It appears Defendants main attack on *Hidajat* goes to the weight, "Importantly, Hidajat did not control for smoking, a class 1 known human carcinogen according to the International Agency for Research on Cancer (IRAC)." (Def. Br. at 16). This is not true, as quoted just below. Defendants then remove all doubt that their attack goes to the weight by asserting "Hidajat's failure to control for this key confounding variable substantially ***diminishes the study's value***". (Def. Br. at 17 (emphasis added)). Dr. Etminan was well aware of the strengths and weaknesses of *Hidajat*, which he detailed in his expert report – including that the authors addressed smoking:

> While the study did control for the cofounding effect of age, it did not directly control for smoking, a variable also associated with cancer. **However, the authors acknowledged that simulations using smoking in the data did not change the results**. Moreover, an unmeasured confounder—a confounder that could not be measured in the study (e.g. family history of cancer), would need to have a strong effect to change the results for the 10 different cancers reported by *Hidajat*.

(Etminan Report at 15 (emphasis added)). Dr. Etminan even utilized E-value methodology to create a table that identified the magnitude of the hazard ratio an unmeasured confounder would have to achieve in order to reverse the elevated hazard ratios for each cancer type identified in *Hidajat* (an astonishingly high 2.7-10.1 hazard ratio of an unmeasured confounder would be needed to reverse the findings of *Hidajat*). (Etminan Report at 15). Dr. Etminan also applied the E-value methodology to *Hidajat* in the same reliable manner he does outside of litigation:[8]

> I used the E-value methodology which I had – I have used actually before in my – in my research studies. I just wanted to do another search just to see if there is any newer or perhaps better methodology than the E-value methodology. And I found that there isn't any, so I used the method that I have used, you know, a number of times in the past in my own research.

(Etminan Dep. Tr. Vol. I, 87:2-11).

[8] Defendants claim Dr. Etminan's entire analysis should be called into question due to his application of the E-value methodology (Def. Br. at 17).

Defendants also attack Dr. Etminan for relying on *Hidajat* because the route of NDMA exposure was inhalation. (Def. Br. at 16). Dr. Etminan explained in his deposition:

> The question that I addressed was: Does exposure to NDMA and exposure would mean NDMA that gets in to the body systemic – systemically absorbed NDMA, which can be through oral, inhalation, skin. I think mainly those are the – the main routes of the exposure. Does builds – does exposure to NDMA through any of those routes that make it systemic in the body cause cancer.

(Etminan Dep. Tr. Vol. I, 56:11-19). Additionally, *Hidajat* provides evidence as to what organs are susceptible to cancer formation if orally ingested NDMA clears the liver and reaches systemic circulation. Testimony from Dr. Bottorff, Defendants' pharmacist, demonstrates that orally ingested NDMA at the levels in valsartan can clear the liver. Dr. Bottorff testified that orally ingested NDMA is fully saturating and exceeding the capacity of the liver if it is detected in the blood, that the average American diet contains a few hundred nanograms of NDMA, and finally that "it has been reported that NDMA and NDEA were present in human peripheral blood samples and that the amounts increased after a meal."[9] (Bottorff Dep. Tr. 154:17-21, 176:5-8, 247:21-248:22, 250:9-18, 257:21-24, Ex. J). Similarly, Plaintiffs' expert Dr. Panigrahy, a cancer researcher opined:

> **Oral bioavailability is defined as the amount of NDMA that reaches the systemic blood circulation which can transport the NDMA to various tissues throughout the body**. The **bioavailability of NDMA is higher in larger experimental animals** compared to rodents, suggesting that NDMA's potent cancer-causing activity observed in rodents can be even more aggressive and **lead to many more tumor types in humans. The level of NDMA in the blood following oral administration is primarily controlled by the amount metabolized in the liver.** The fraction of an orally administered dose of NDMA that can be detected in blood (compared to I.V. administration) has been investigated in a number of different species. For example, approximately 8% of an orally administered dose was accounted for in the blood of the rat and hamster, while 49%, and up to 93%, of the administered dose was bioavailable in the money (49%), pig (67%), or dog (93%). Thus, a high percentage of an orally administered

[9] If dietary NDMA is already fully saturating the liver, then any additional NDMA consumed via valsartan would enter systemic circulation.

> dose of NDMA passes through the liver into the systemic circulation in larger species such as dogs and monkeys compared to smaller species such as rodents.[10]

(Panigrahy Report at 78, Ex. K).

As such, *Hidajat* not only quantifies NDMA exposure more accurately than any other epidemiological study, *Hidajat* is most on point study as to which organs in humans are at an increased risk of cancer due to NDMA exposure.

G. Background NDMA Exposure is a Red Herring

Defendants claim that their criticism of Dr. Etminan "failing to account for baseline NDMA or NDEA exposure from endogenous (internally generated) and exogenous (external) sources" is evidence of a flawed methodology. (Def. Br. at 2). None of the epidemiological studies measured endogenous NDMA formation, and in deposition Dr. Etminan explained that there isn't an accurate way to measure endogenous formation of NDMA and that endogenous formation of NDMA should be fairly uniform from one individual to another:

> It's very difficult to quantify and ascertain endogenous NDMA exposure. I'm not familiar with any sort of robust gold standard, if you will, method to do it, because it's so complex. But then again back to what we discussed before, endogenous NDMA, you have to have a good reason why one group – endogenous NDMA can be – we can all be exposed to endogenous NDMA. It's a very complex sort of process to quantify. But then, again, how can we actually say that one group in this study is exposed to more endogenous NDMA than the other? And that's – and why – and there's no reason to believe that's the case.

(Etminan Dep. Tr. Vol. I, 114:1-16). Dr. Etminan continued, explaining that, "there is no reason to believe that the controls in the cases vary very differently coming from the same sort of population in terms of endogenous NDMA exposure. (Etminan Dep. Tr. Vol I, at 116:9-13).

Furthermore, the epidemiological studies that Dr. Etminan relied on compared the risk of cancer among those exposed to the highest levels of NDMA to those exposed to the lowest levels.

[10] Unlike Plaintiffs' experts, Defendants' experts are of the opinion that humans are more like rats than monkeys in how they metabolize NDMA and NDEA.

(Etminan Report at 15-16). Comparing those exposed to the highest levels of NDMA to those exposed to the lowest levels of NDMA would inherently control for background rates of NDMA exposure.

Defendants appear to think that Dr. Etminan's statement that "[I]t is impossible to identify subjects with absolutely no exposure to NDMA as this agent is ubiquitous in the environment and thus some level of exposure is always expected" was an admission. (Def. Br. at 10). What Defendants apparently fail to realize is that as the unavoidable background rate of NDMA increases, less NDMA is needed in a pill of valsartan to push an individual over the "threshold" for NDMA to cause cancer, assuming there even is a threshold. Defendants need to look no further though than the deposition transcript of their own epidemiologist, Dr. Fryzek, who when asked if the FDA's 96ng limit included exposure that humans get through their diet, Dr. Fryzek responded, "I assume it's exposure in the diet, endogenous exposure, et cetera." (Fryzek Dep. Tr. 436:17-437:18).

Dr. Etminan considered the background rates of NDMA exposure, and the epidemiological studies he relied on adequately controlled for background rates of NDMA exposure.

H. Dr. Etminan's NDEA Opinions Are Supported by the Totality of Evidence

Defendants request that Dr. Etminan be precluded from offering any opinions specific to NDEA causing esophageal, stomach, colorectal, liver, lung, bladder, prostate, blood, or pancreatic cancers,[11] claiming that "Dr. Etminan's causation opinions with respect to NDEA are *devoid of any support* in the scientific literature.[12] (Def. Br. at 25 (emphasis added)). Dr. Etminan actually starts by explaining that an epidemiologic study by *Zheng* found:

[11] Defendants did not seek to preclude Dr. Etminan from offering any opinions specific to NDMA causing esophageal, stomach, colorectal, lung, or prostate cancers. (Def. Br. at 30).
[12] NDMA has been studied far more extensively than NDEA.

> A 128% increase in the risk of pancreatic cancer among those exposed to the highest intake of NDEA. The highest level in this study was defined as 120ng/1000Kcal/day vs. the lowest category of 40ng/1000Kcal/day. **This means that some of the valsartan batches that have NDEA levels measured as high as 5,417.9ng (per 320mg table[t]) would have approximately 22 times higher (computed based on a 2000Kcal/day diet) NDEA amount than the highest category measured in the study by *Zheng***.

(Etminan Report at 20).

While Defendants correctly note that the authors of *Zheng* recommended a careful examination of *potential mechanisms* in which NDEA can cause cancer before concluding that NDEA is carcinogenic in humans, they then incorrectly claim that "Dr. Etminan states in conclusory fashion, *citing no authority*" when opining that given NDEA's "carcinogenic profile, especially the substantial similarity in the mechanism of action of NDEA in causing cancer to NDMA, it would be expected that NDEA also has the potential to cause the other 8 cancers [in addition to pancreatic cancer] associated with NDMA." (Def. Br. at 27, 28 (emphasis added)); Etminan Report at 32). In reality, Dr. Etminan has a section in his report on NDEA carcinogenicity, where he cites to the Unites States Environmental Agency (USEA) classification of NDEA as a probable carcinogen, multiple studies demonstrating NDEA to be a cancer initiator, and literature on NDEA being used to induce cancer in animals via cellular genotoxicity and direct chromosomal damage to the DNA. Dr. Etminan then cites additional studies and authority, noting "NDEA has also shown to increase the risk of cancerous tumors in animals and its daily allowable limit is even lower (1/3, 26.5ng vs 96.0) compared with NDMA suggesting its higher carcinogenic potential (FDA)." (Etminan Report at 7).

Consideration of the totality of scientific evidence to support a carcinogenicity causation determination is not only accepted but preferred. In the *Reference Manual on Scientific Evidence; Reference Guide on Epidemiology*, by Michael Green, et.al, Third Edition, 2011 by the Federal Judicial Center, a reference work frequently cited and relied upon by federal courts, there is a

citation to *Modern Criteria to Establish Human Cancer Etiology,* by Carbone, 64 Cancer Res. 5518, 5522 (2004) stating "There should be no hierarchy [among different types of scientific methods to determine cancer causation]. *Epidemiology, animal, tissue culture and molecular pathology should be seen as integrating evidences in the determination of human carcinogenicity*". (emphasis added).[13] This is exactly the methodology followed by Dr. Etminan to support his opinions and why his analysis is scientifically based and reliable.

III. DEFENDANTS' ARGUMENTS GO TO THE WEIGHT OF THE OPINIONS

Defendants' arguments, primarily based on mischaracterizations of Dr. Etminan's expert report and deposition testimony, at most go to the conclusions reached and the weight to be given to those conclusions. This is not a permissible attack under *Daubert*. The focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions. *Glynn* at *2 (citing *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594-95 (1993)). The basis for this Court's finding that an expert should be precluded under *Daubert* in another case demonstrates by comparison why Dr. Etminan's opinions should not be impacted here. *Player v. Motiva Enterprises LLC*, 2006 WL 166452, at *6-7 (D.N.J. January 20, 2006) (citations omitted) (Ex. L). In *Player*, this Court found an expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things. *Id.* at *7. This Court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer-reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8. None of those things can be said about Dr. Etminan's opinions. Defendants make no attack on Dr. Etminan's qualifications; however, the extent and frequency in which Defendants misrepresent the contents of Dr. Etminan's expert report and deposition testimony only further

[13] A free PDF of the manual is available at the following link: https://tinyurl.com/2bu96z7f.

illustrate the strength of Dr. Etminan's opinions and Plaintiffs case in general.

CONCLUSION

For the foregoing reasons, Defendants' motion to preclude Dr. Etminan's opinions under *Daubert* should be denied. Dr. Etminan is well-qualified, and applied a valid methodology, relying on peer-reviewed literature. Defendants' criticisms of Dr. Etminan go to the weight to be accorded to his testimony, at most, and can be exposure fully on cross-examination at trial.

Dated: December 1, 2021

Respectfully,

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CERTIFICATE OF SERVICE

I hereby certify that on December 1, 2021, I electronically filed this brief and my supporting certification with the Clerk of the Court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL. In addition, I hereby certify that unredacted copies of foregoing document will be served contemporaneous to filing via email on the Court, Special Master, and the Defense Executive Committee at DECValsartan@btlaw.com.

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By: /s/ C. Brett Vaughn

Dated: December 1, 2021